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Your reference
HBD/DG/GR2143

26 JUL 1995

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The Patent Office

Request for grant of a Patent

Form 1/77

Patents Act 1977

1 Title of invention

1 Please give the title of the invention

METHOD AND APPARATUS FOR FILLING CAVITIES

2 Applicant's details

☑ First or only applicant

2a If you are applying as a corporate body please give:

Corporate name
GLAXO GROUP LIMITED

Country *(and State of incorporation, if appropriate)*
GREAT BRITAIN

2b If you are applying as an individual or one of a partnership please give in full:

Surname

Forenames

2c In all cases, please give the following details:

Address
GLAXO HOUSE
BERKELEY AVENUE
GREENFORD
MIDDLESEX

UK postcode *(if applicable)* UB6 0NN

Country GREAT BRITAIN

ADP number *(if known)* 473587002

4 Reference number

4 Agent's or applicant's reference number *(if applicable)* HBD/DG/GR2143

5 Claiming an earlier application date

5 Are you claiming that this application be treated as having been filed on the date of filing of an earlier application?

Please mark correct box

Yes- ☐ No ☒ ➡ *go to 6*

⬇ *please give details below*

☐ number of earlier application or patent number

☐ filing date *(day month year)*

☐ and the Section of the Patents Act 1977 under which you are claiming:

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15(4) (Divisional) ☐ 8(3) ☐ 12(6) ☐ 37(4) ☐

6 Declaration of priority

6 If you are declaring priority from previous application(s), please give:

If you are declaring priority from a PCT Application please enter 'PCT' as the country and enter the country code (for example, GB) as part of the application number.

Please give the date in all number format, for example, 31/05/90 for 31 May 1990.

Country of filing	Priority application number *(if known)*	Filing date *(day,month,year)*

2d, 2e and 2f:
If there are further applicants please provide details on a separate sheet of paper.

Second applicant (if any)

2d If you are applying as a corporate body please give:

Corporate name

Country *(and State of incorporation, if appropriate)*

2e If you are applying as an individual or one of a partnership please give in full:

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3
An address for service in the United Kingdom must be supplied.
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3 Address for service details

3a Have you appointed an agent to deal with your application?

Yes [X] No [ ] ➡ *go to 3b*

⬇ ***Please give details below***

Agent's name
HUGH B DAWSON
Agent's address
GLAXO HOUSE
BERKELEY AVENUE
GREENFORD
MIDDLESEX
Postcode UB6 0NN

Agent's ADP number 06074733001

3b:
If you have appointed an agent, all correspondence concerning your application will be sent to the agent's United Kingdom address.

3b If you have not appointed an agent please give a name and address in the United Kingdom to which all correspondence will be sent:

Name

Address

Postcode

ADP number *(if known)*

Daytime telephone number *(if available)*

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(See Page 2 No. 3a)

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The answer must be 'No' if:
- *any applicant is not an inventor*
- *there is an inventor who is not an applicant, or*
- *any applicant is a corporate body.*

7 Inventorship

7 Are you (the applicant or applicants) the sole inventor or the joint inventor?

Please mark the correct box

Yes ☐ No ☒ ➡

A statement of Inventorship on Patents Form 7/77 will need to be filed (see Rule 15).

8

Please supply duplicates of claim(s), abstract, description and drawing(s).

8 Checklist

8a Please fill in the number of sheets for each of the following types of document contained in this application.

Continuation sheets for this Patents Form 1/77	1		
Claim(s)		Description	9
Abstract		Drawing(s)	3

8b Which of the following documents also accompanies the application?

Please mark correct box(es)

Priority documents *(please state how many)*	
Translation(s) of Priority documents *(please state how many)*	
Patents Form 7/77 - Statement of Inventorship and Right to Grant *(please state how many)*	
Patents Form 9/77 - Preliminary Examination/Search	
Patents Form 10/77 - Request for Substantive Examination	

9

You or your appointed agent (see Rule 90 of the Patents Rules 1990) must sign this request.

9 Request

I/We request the grant of a patent on the basis of this application.

Please sign here ➡ Signed **Hugh B. Dawson Agent for the Applicant** Date 24/07/1995 *(day month year)*

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4 Reference number

4 Agent's or applicant's reference number *(if applicable)* HBD/DG/GR2143

5 Claiming an earlier application date

5 Are you claiming that this application be treated as having been filed on the date of filing of an earlier application?

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Yes- ☐ No ☒ ➡ *go to 6*

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15(4) (Divisional) ☐ 8(3) ☐ 12(6) ☐ 37(4) ☐

6 Declaration of priority

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Please give the date in all number format, for example, 31/05/90 for 31 May 1990.

6 If you are declaring priority from previous application(s), please give:

Country of filing	Priority application number *(if known)*	Filing date *(day,month,year)*

METHOD AND APPARATUS FOR FILLING CAVITIES

This invention relates to a method and apparatus for filling cavities with powder in free flowing agglomerated micronised form. More particularly, it relates to a method and apparatus for controlling the flow of such powder for filling small cavities. The invention has particular application to the situation where the cavities are defined by pockets formed in a dosing disc to hold doses of medicament in powder form, for example medicament which is to be inhaled by a patient, but it is also applicable to cavities defined in other ways and for alternative applications.

It has been found that medicaments for administration by inhalation should be of a controlled particle size in order to achieve maximum penetration into the lungs, preferably in the range of 1 to 10 micrometres in diameter. Unfortunately, powders in this particle size range, for example micronised powders, have very poor flow characteristics due to the cohesive forces between the individual particles which make them readily agglomerate together to form bridges which are not readily broken apart to become free flowing. These characteristics create handling and metering difficulties which adversely affect the accurate dispensing of doses of the powder.

When handling medicament in powder form it is essential to prevent contamination of the powder. It is therefore necessary to keep the powder isolated as far as possible from moving machinery which might otherwise introduce the risk of contamination by lubricants or shavings produced as a result of wear and tear of the machinery.

DE 3607187 discloses an apparatus for supplying particles in fine dust form in measured doses. Powder is supplied from a hopper to a vibrator with an outlet. The hopper uses an agitator and compressed air to maintain the powder in a dry and deagglomerated form. The vibrator/outlet unit allows an approximate control of flow of the powder onto a rotating dosing plate underneath, provided with a ring of pockets in

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a hopper for containing the said powder adapted to be situated above at least one of the cavities to be filled, the said hopper being provided with means for controlling flow of powder into the cavity, wherein the hopper has at least one outlet of such a size and configuration as to prevent flow of the powder therethrough when in a static state and to allow flow of the powder when subject to vibration, and that the means for controlling flow of powder into the cavity comprises a vibrating means.

Suitably, the frequency of vibration is in the range from 1Hz to 1000Hz. More suitably the frequency of vibration is in the range from 27Hz to 50Hz.

Suitable amplitudes of vibration are between 0.02mm and 2.00mm. Preferable amplitudes of vibration are between 0.2mm and 1.0mm.

The invention further provides an apparatus for filling a plurality of closely spaced small cavities wherein the hopper has a plurality of closely spaced outlets adapted to be situated above the said plurality of closely spaced small cavities.

Suitably, the at least one outlet is in the form of a funnel terminating in at least one hole.

More suitably, the at least one outlet comprises a substantially horizontal pathway leading to an outlet hole.

The invention will now be described with reference to the accompanying drawings, in which:

Figure 1 is an isometric view showing an embodiment of the apparatus according to the invention;

Figures 2 a-d show in section a multiple hopper and dose cavity ring according to a second embodiment of the invention at different stages during the filling process;

its upper surface, the pockets being filled with powder as they pass underneath the outlet. As the dosing plate rotates, a doctor blade wipes excess powder from the upper surface, and the doses of powder in the pockets are removed and supplied to an intended use station by means of a suction tube.

US 4688610 discloses an apparatus for accurately dispensing programmed weights of particulate solids which tend to agglomerate. Again, powder is supplied from a hopper with an agitator to a vibrating conveyor and on to a discharge area. A microprocessor controller is used to control the activation of the agitator and vibrator to dispense precisely weighed quantities of the particulate solids.

By careful sizing of agglomerated micronised powder it is possible to make use of the cohesive forces between the particles to create agglomerates of powder which are free flowing. However, such agglomerates are easily destroyed by physical contact with other bodies, though exposure to vibrations does not adversely affect them. Careful handling is therefore required to take advantage of the free flow characteristics.

It is an object of the invention to provide a method and apparatus for conveniently controlling flow of powder in free flowing agglomerated micronised form for filling small cavities while keeping physical interaction with the powder to a minimum.

According to the invention there is provided a method of filling a cavity with a quantity of powder in free flowing agglomerated micronised form, which comprises feeding the agglomerated micronised powder from a hopper into the cavity situated beneath the hopper, whereby the powder may be made to flow from the hopper by subjecting it to vibration and the flow may be stopped by cessation of vibration.

The invention also provides an apparatus for filling cavities with a quantity of powder in free flowing agglomerated micronised form which comprises

The dose ring is mounted such that the face presenting the cavities is uppermost, with one or more of the cavities situated underneath the outlet from the hopper.

The carrier 4 comprises a turntable which may be rotated by means of a variable speed motor 7 and drive belt 8. A doctor blade 9 is mounted for pivotal movement such that it may swing between a first position (as shown in Figure 1) in which it is clear of the dose ring 3 and a second position (not shown) in which it lies across part of the upper face of the dose ring 3 traversing from the periphery across the region presenting the cavities. In the second position the doctor blade 9 is held just above the face of the dose ring 3.

To fill the cavities, micronised drug powder, such as zanamivir powder, is sized using a conventional sieving process such that the largest axial dimension across each agglomerate is up to 500 microns. As the hopper assembly fills, the powder forms a bridge at the hopper outlet which prevents flow of the powder through the outlet. To make the powder flow from the hopper out of the outlet the linear vibratory feeder 2 is set to vibrate the hopper assembly 1 with an amplitude of between 0.2mm and 0.4mm and with a vibratory frequency conveniently of around 50Hz. The vibrations break the powder bridge and prevent the powder from rebridging. In the absence of a bridge, the powder flows freely out of the outlet and falls onto the periphery of the dose ring 3 underneath the outlet. The dose ring 3 is also subjected to similar vibrations from the rotary vibratory feeder 6 whilst simultaneously being made to rotate slowly by virtue of carrier 4, motor 7 and drive belt 8. The effect of the vibrations is to cause the cavities at the periphery of the dose ring 3 to fill uniformly with powder as they pass underneath the hopper outlet while the dose ring 3 slowly rotates. The vibrations also help to cause excess powder in the cavities and on the upper face of the dose ring 3 to move along the face to the next cavity or to fall off the edge of the dose ring 3 and into the powder collecting pot 5. The size of the outlet hole allows rapid flow of powder out of the hopper, and the speed of rotation is set according to the flow rate of powder through the hopper outlet and the

Figures 3a, 3b, 3c and 3d are a plan view, a section along line A-A of figure 3a, an underside view and a section along line X-X of figure 3a showing a multiple hopper according to a third embodiment of the invention.

Referring first to Figure 1, this shows a powder hopper assembly 1 fixed to a linear vibratory feeder 2 which has its own controller enabling the adjustment of the vibratory amplitude to a given level. The powder hopper has a funnel section at its lower end with an inclusive angle of 90° terminating at an outlet hole of 3mm diameter. Positioned below the hopper is a dose ring 3 mounted on a carrier 4 which in turn is mounted on a head 5 incorporating a powder collecting pot. The head 5 is fixed to a rotary vibratory feeder 6 which has its own controller enabling adjustment of vibratory amplitude and frequency. The dose ring 3 comprises a flat disc with a plurality of cavities formed in one face in a circle coaxial with that of the dose ring and close to its periphery.

The dose ring is suitable for carrying a plurality of doses of powdered medicament suitable for inhalation and is adapted for use in a powder inhalation device. Powdered medicaments suitable for this purpose are, for example, for the treatment of asthma, and include salbutamol, beclomethasone, salmeterol, fluticasone, formoterol, terbutaline, budesonide and flunisolide, and physiologically acceptable salts, solvates and esters or any combination thereof. Preferred medicaments are salbutamol, salbutamol sulphate, salmeterol, salmeterol xinafoate, fluticasone propionate, beclomethasone dipropionate and terbutaline sulphate. Other suitable powdered medicaments include antiviral medicaments, for example zanamivir (4-guanidino-Neu 5Ac 2en). A dose may be constituted from the contents of one or more cavities and the size of each cavity will depend on the dose to be delivered. It is to be understood that the medicament powder may consist purely of one or more active ingredients, or there may additionally be a carrier, for example lactose powder.

Figures 2a-2d show a hopper 11 and dose ring 12 suitable for use in a second embodiment of the invention. The dose ring is similar to the dose ring described with reference to figure 1. Hopper 11 is in the form of a multi-dose feeder ring which presents a ring shaped channel 13 for carrying the powder to be fed to the dose ring 12. At its lower end the walls of the channel converge with an inclusive angle of 90°, terminating with a plurality of outlet holes 14 arranged in pairs which align with the cavities in the dose ring 12 when the dose ring is presented to the hopper as shown in fig 2b, each hole being of 1.0mm diameter.

To fill the cavities using the apparatus of the embodiment shown in figures 2a-2d, hopper 11 is fed with free flowing agglomerated micronised zanamivir powder 15 which has been sized in the same way as the powder discussed with reference to figure 1. As the hopper fills, the powder 15 forms a bridge at each of the hopper outlets 14 which prevents flow through the outlets. An empty dose ring 12 is presented to hopper 11 with its cavities uppermost and locked into engagement with the hopper 11 such that outlets 14 each align with a respective cavity in the dose ring 12 (figs 2a and 2b).

The dose ring and hopper assembly is then subjected to vibration of a frquency of between 27Hz and 33Hz and an amplitude of between 0.25mm and 1.0mm which breaks the powder bridges at each of the outlets 14 causing powder to flow freely out of the outlets with a constant flowrate into the cavities beneath (fig. 2c).

The size of the outlet holes ensures a constant and controllable flow of powder from the hopper, making it possible to volumetrically fill the cavities by regulating the duration of the vibration. Thus, vibration is applied to the dose ring and hopper assembly for a predetermined time until the cavities are sufficiently filled, at which point the vibration is stopped and the powder in the hopper bridges over each of the outlet holes 14, so preventing any further flow of powder from the hopper. The filled dose ring 12 is then lowered away from the hopper 11 (fig. 2d) and

size and density of the cavities about the dose ring 3, the intention being to ensure that each cavity will receive more than enough powder to fill it as it passes under the hopper outlet.

During the cavity filling process the doctor blade 9 is moved into its second position as described above and moves over the upper face of the dose ring 3 as the dose ring rotates to push away any powder remaining on the upper face and to remove any overfill of powder in the cavities. Powder removed from the upper face of the dose ring 3 by the doctor blade 9 is deposited in the powder collecting pot 5 and may be recycled.

When all of the cavities in the dose ring 3 have been filled, usually after one complete revolution of the dose ring 3, the linear vibratory feeder 2 is switched off and the powder flow through the outlet hole of the hopper stops almost instantaneously through the formation of a powder bridge at the outlet.

The dose ring is allowed to complete a further revolution to ensure that the upper face of the dose ring is wiped clean of powder by the doctor blade 9. Once the upper face of the dose ring is clean the doctor blade 9 is moved away from the dose ring 3 into its first position as described above, and the filled dose ring 3 may be removed from carrier 4 and replaced with an empty dose ring for filling. For use in an inhalation device the dose ring is adapted such that the cavities may be sealed against powder loss, moisture ingression etc by means of a cover layer secured by heat sealing, adhesive or other fastening means, or through sliding contact of the upper face of the dose ring with the housing or other element of the device. Failure to provide a clean surface is likely to lead to defective sealing, and use of the doctor blade as described ensures that the surface is free from powder, so obviating the need for further preparation of the upper surface prior to assembly into the device or application of a cover layer. However, it is to be understood that other means of cleaning the upper surface of the dose ring may be used, for example a low pressure air jet.

the same way as described in relation to the embodiment shown in figures 2a-2d. The dose ring and hopper assembly is then subjected to rotary vibration which causes powder on the floor 28 of the horizontal section 26 of each of the outlet pathways to flow and fall through the outfeed slots 27 into the cavities beneath as more powder flows into the outlet pathway from hopper 21 through outlet slots 24. The flowrate of powder into the cavities is fairly constant provided the amplitude and frquency of vibration remain constant so fill weight can be accurately measured by careful timing of the duration of vibrator operation.

When the cavities are full, the vibration applied to the dose ring and hopper assembly is stopped and flow of powder into the cavities ceases. The filled dose ring is lowered away from the hopper and may be replaced by an empty dose ring for filling in the same way as described with reference to figures 2a-2d.

It will be appreciated that whilst the apparatus described with reference to the figures are specifically designed for filling cavities in a circular configuration, the invention could equally be applied with obvious modifications to the filling of cavities in any other configuration such as a long strip or a rectangular array of cavities in a dose ring.

It will further be appreciated that whilst the dimensions, vibration frequencies and amplitudes described herein with reference to the figures give good results with zanamivir powder, it may be appropriate to vary these values according to the characteristics of the powder being used.

may be replaced by an empty dose ring for filling. As the dose ring 12 is lowered away from the hopper 11 the upper face of the dose ring remains clean of powder and the filled dose ring is ready for assembly into the inhalation device or application of a cover layer.

The embodiment of the invention as described with reference to figures 2a-2d has the advantages of not requiring a doctor blade, powder collecting pot or an arrangement for rotating the dose ring during the filling process. It may also offer a faster method of filling the dose ring than that provided by the embodiment shown in figure 1 as each cavity is filled simultaneously.

Referring now to figures 3a-3d, these show an alternative hopper design to that shown in figures 2a-2d. Hopper 21 is again in the form of a multi-dose feeder ring which presents a ring shaped channel 23 for carrying the powder to be fed to the dose ring (not shown). The floor of the channel is provided with ten outlet slots 24 each of 2mm width. As is best seen in figure 3d, each slot provides the entrance to one of ten outlet pathways each comprising a first substantially vertical section 25 followed by a second substantially horizontal section 26 and terminating in an outfeed slot 27.

In use, hopper 21 is fed with free flowing agglomerated micronised powder 29 as described with reference to figures 2a-2d. The powder flows through outlet slots 24 and rests on the floor 28 of the horizontal section 26 of each of the outlet pathways. Due to the natural angle of repose A of the powder 29 (fig 2d) and the vertical offset of the outfeed slots 27 from the outlet slots 24 the powder does not naturally flow out of outfeed slots 27 as hopper 21 fills. It will be understood that the vertical offset of the outfeed slots 27 from the outlet slots 24 may be adjusted to suit the natural angle of repose of the powder intended to be used.

An empty dose ring is presented to the underside 22 of hopper 21 with its cavities uppermost and locked into engagement with the hopper 21 such that outfeed slots 27 each align with a respective cavity in the dose ring in

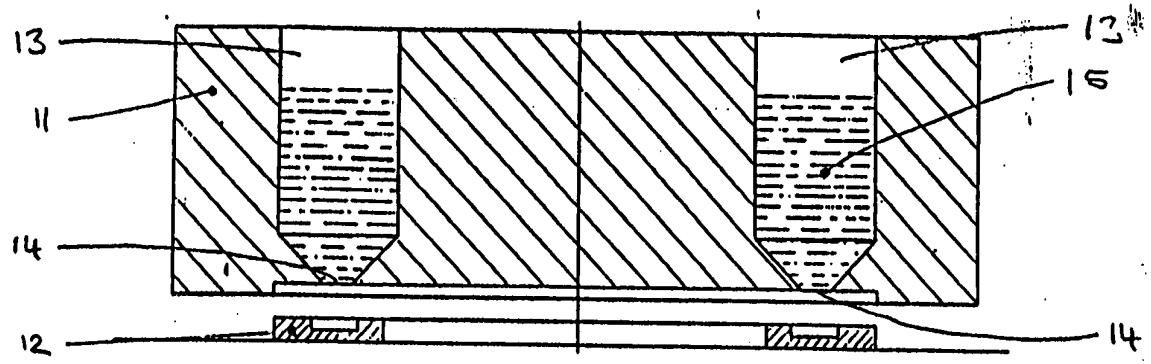


FIG. 2a

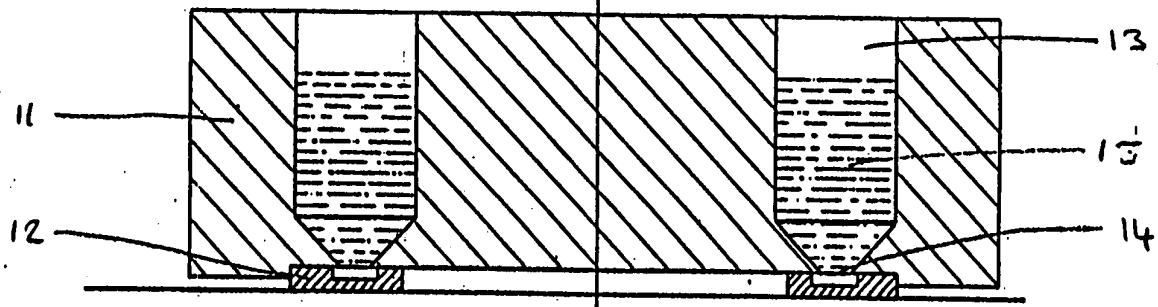


FIG 2b

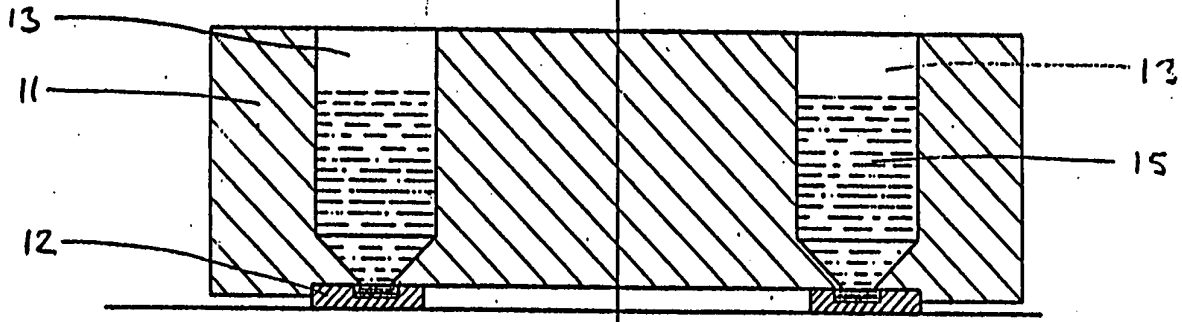
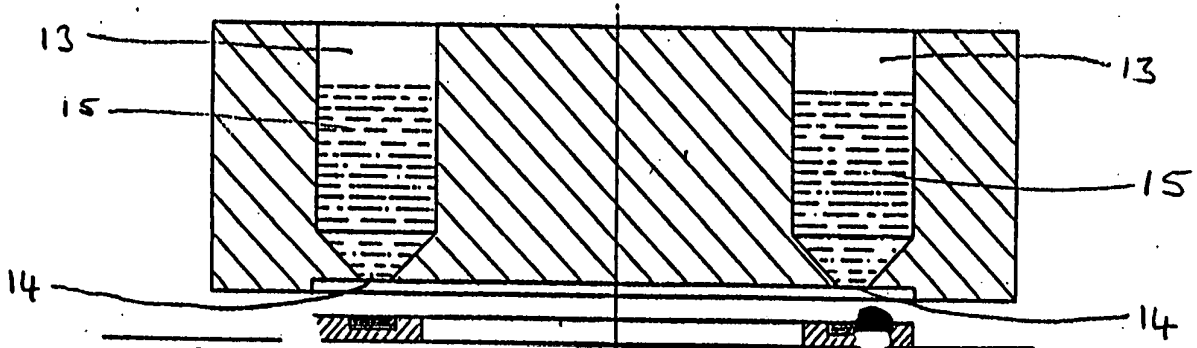


FIG 2c



2d

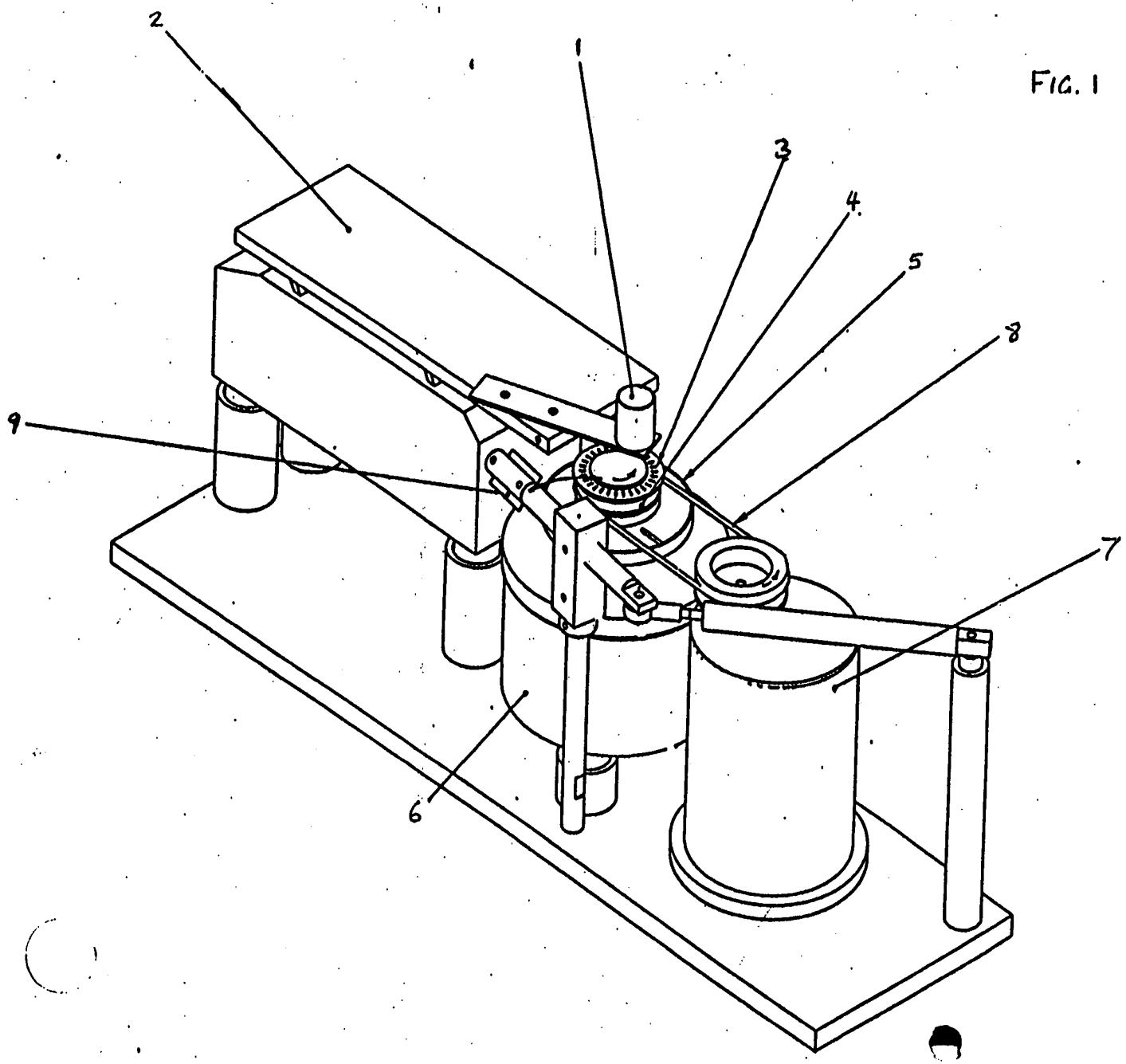


FIG. 1

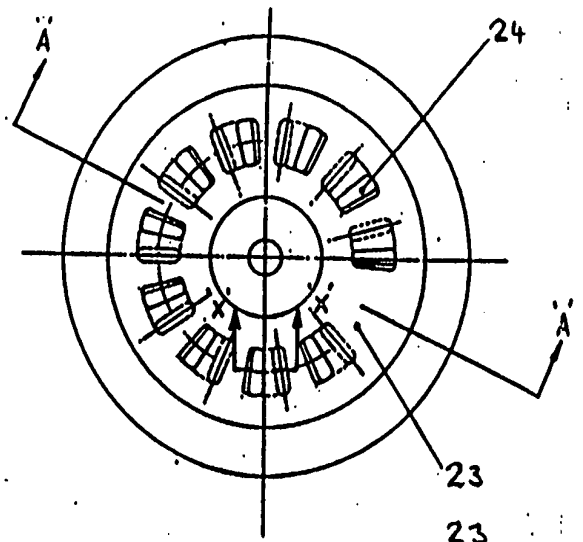


FIG 3a

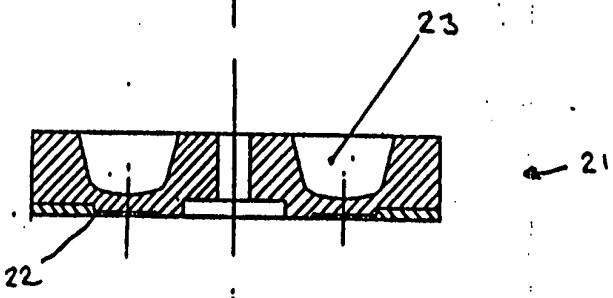


FIG 3b

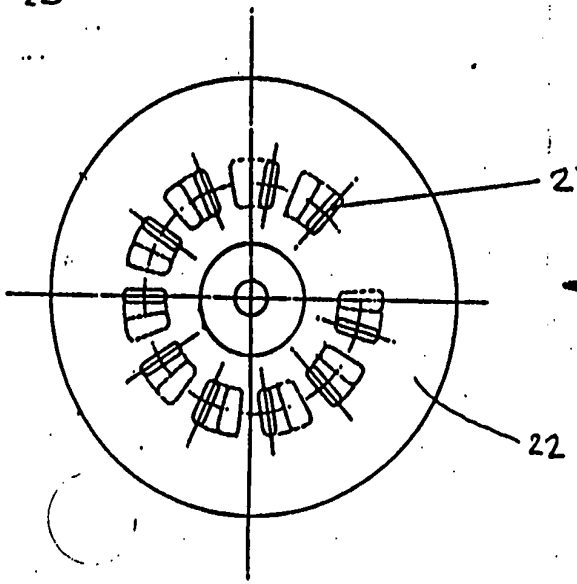


FIG 3c

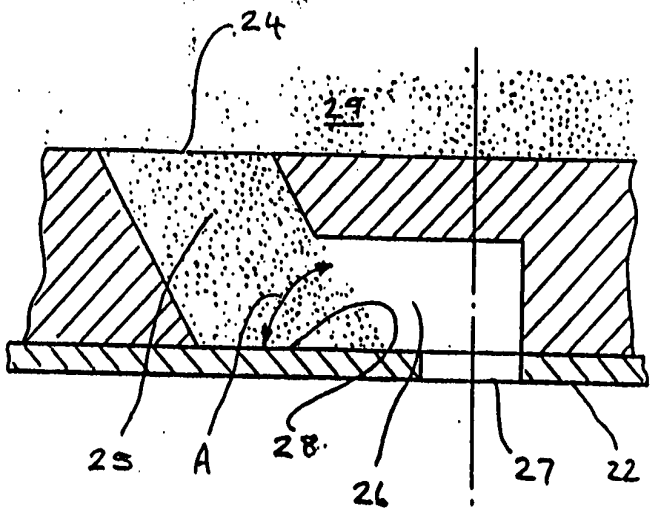


FIG 3d